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‘Stressing’ rodent self-grooming for neuroscience research

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We appreciate the thoughtful Correspondence by Fernández-Teruel and Estanislau on our Review (Neurobiology of rodent self-grooming and its value for translational neuroscience. *Nat. Rev. Neurosci.***17**, 45–59 (2016))[1], which raises the issue of the relationship between stress and self-grooming (Meanings of self-grooming depend on an inverted U-shaped function with aversiveness. *Nat. Rev. Neurosci.* http://dx.doi.org/10.1038/nrn.2016.102 (2016))[2]. We agree that the effect of stress on self-grooming can often be described as an inverted U-shaped function: self-grooming typically occurs spontaneously at low arousal (as a maintenance behaviour), becomes longer (and may alter in pattern) during moderate arousal (as a ‘displacement activity’) and can be inhibited by high-stress states that elicit freezing, fight or flight responses[1–4].

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Competing interests statement

The authors declare no competing interests.

However, despite the usefulness of this view, caution is needed because the relationship between stress and self-grooming can be more complex, and self-grooming duration measures in relatively mild stress (the main behavioural measures and situations discussed in the Correspondence[2]) alone may be insufficient for adequate neurobehavioural analyses of rodent self-grooming[1,3,4]. For example, high-frequency, short bouts of self-grooming can yield a cumulative duration that is similar to that of fewer, longer bouts of such behaviour. Moreover, rats that exhibit different self-grooming durations may show no differences in anxiety-related behavioural or neuroendocrine parameters[5]. In addition, as self-grooming frequency (the rate of initiation) and bout length (execution) under stress probably have differential neural underpinnings, these aspects of self-grooming may differentially change during stress (BOX 1). Even when different groups of rodents show similar times spent self-grooming under conditions of stress, they may exhibit altered self-grooming body targets (that is, rostral face versus caudal body and tail regions)[1]. Indeed, mounting evidence suggests that the behavioural microstructure of rodent self-grooming may serve as a sensitive marker of stress levels[1] (BOX 1). Therefore, a more detailed measure of self-grooming behaviour — incorporating the average bout duration, the transitions between stages, the number of interrupted or incomplete bouts and other ethologically derived parameters[1] — can help to provide significant insights into the nature of self-grooming phenotypes under different levels of stress or arousal.

It may also be important to recognize that low–moderate–high arousal and self-grooming continuums in various behavioural contexts may not ‘flow’ as tightly as can be assumed[3,4]. For example, self-grooming bouts can occur immediately in anticipation of, or right after, exposure to a stressful stimulus (for example, self-grooming in voles occurs first after predator fright, before locomotion[3,4]; BOX 1). Thus, this raises the possibility of rethinking the acute stress response in rodents as ‘freeze, fight, flight and groom’. Namely, self-grooming evoked by high-stress situations may differ considerably — both behaviourally and mechanistically — from low-arousal ‘comfort’ and moderate-arousal (for example, novelty-evoked) self-grooming[1]. Moreover, although high-stress self-grooming is often associated behaviourally with freezing, fight or flight[2] (BOX 1), it is currently unclear whether all of these behaviours are mediated by shared ‘high-stress’ neural circuits or compete with each other and with self-grooming for circuitry and motor movements.

In summary, we agree that stress modulates rodent self-grooming behaviour in ways that often follow an inverted-U relation[2], but we also note that this crucial relationship may be more complicated. Given the emerging relevance of self-grooming in the modelling of various affective brain disorders, the analysis of this important relationship will benefit from focusing on multiple (rather than single) self-grooming behavioural measures, an appreciation of a wider spectrum of specific biological contexts in which self-grooming occurs and an in-depth analysis of its underlying neural circuitry[1].

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Box 1

The emerging complexity of rodent self-grooming during stress

Rodent self-grooming frequency and duration may differentially change during stress

- Restraint-induced stress increases the duration but not the frequency of self-grooming in wild-type mice, although such stress elevates both the frequency and duration of such grooming in mice lacking period circadian clock 1 (*Per1*), an acute stress response effector gene[6]
- Alcohol-preferring (AA) rats, which show low levels of anxiety-like behaviour, initiate more self-grooming bouts than more anxious non-alcohol preferring (ANA) rats[7]

Rodent stress and anxiety may be poorly correlated with self-grooming duration

- Rat subcohorts selected on the basis of self-grooming duration show no differences in anxiety-like behaviours or neurochemical and neuroendocrine parameters[5]
- Acid-sensing (proton gated) ion channel 3 (*Asic3*)-knockout mice show reduced anxiety-like behaviour but increased self-grooming duration compared with wild-type mice[8]
- SH3 and multiple ankyrin repeat domains 3 (*Shank3*)-conditional-knockout mice show increased self-grooming duration compared with wild-type mice; the duration decreases following SHANK3 re-expression without affecting anxiety levels[9]
- BTBR T+tf/J mice show increased self-grooming duration and frequency but normal baseline anxiety and higher stress resilience compared with C57BL/6J mice[10]

Rodent self-grooming behavioural patterning is affected during stress

- The anxiolytic drug clonazepam potently alters both self-grooming activity and sequencing parameters in rats but causes only mild anxiolytic-like effects on other (non-grooming) behaviours[11]
- Overt correlations exist between the number and percentage of correct cephalocaudal transitions of self-grooming and the expression of non-grooming anxiety-related behaviours[11]
- In rats, grooming microstructure is highly sensitive to sleep deprivation-related stress[12]
- Anxious ‘high-yawning’ rats show a higher frequency of rostral self-grooming in novel environments than less anxious ‘low-yawning’ rats[13]

Rodent self-grooming activation in high-arousal, potentially life-threatening stress

- Voles exposed to predator-like overhead stimuli display self-grooming after predator fright, before locomotion[3]
- Saline injection or electric shock evokes elevated self-grooming in mice[14]
- *Asic3*-knockout mice in the resident-intruder test often display stereotypical repetitive self-grooming after fighting[8]
- Mutant mice lacking histidine decarboxylase (*Hdc*) exhibit an increase in tic-like repetitive self-grooming in the conditioned fear paradigm[15]